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## **Childhood growth of singletons conceived following in vitro fertilisation or intracytoplasmic sperm injection**

*a systematic review and meta-analysis*

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Childhood growth of singletons conceived following IVF or ICSI: a systematic review and meta-analysis

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Childhood growth following IVF/ICSI

**ABSTRACT**

**Background**

Assisted reproductive techniques are associated with increased risk of adverse pregnancy outcomes including low birth weight and intrauterine growth restriction. Yet, long-term follow-up on the growth of these children is limited.

**Objective**

To systematically review the literature on post-neonatal height and weight among children conceived following in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment compared to that of children born after spontaneously conception.

**Search Strategy**

A systematic computerized literature search using the online databases Pubmed, Embase, and Scopus.

## **Selection Criteria**

Cohort or case-control studies with an exposed group of singletons conceived following IVF or ICSI along with a control group of spontaneously conceived singletons.

## **Data Collection and Analyses**

Studies were reviewed by at least two authors. Meta-analyses were conducted using Cochrane Review Manager. Quality of the studies was assessed with the Newcastle-Ottawa Scale.

## **Main Results**

Twenty studies were included with 13 of these eligible for meta-analyses. The meta-analyses compared 3,972 IVF/ICSI children with 11,012 spontaneously conceived children and revealed no statistically significant difference in child weight (mean difference (MD) in weight of -160 grams (95% CI: -360; 3)). When stratifying on child age at follow-up, we found a significant lower weight of children 0-4 years old conceived following IVF/ICSI treatment (MD -180 grams (95% CI: -320; -4)), but no longer significant in children from 5 years of age (MD -160 grams (95% CI: -580; 260)). The pooled analysis revealed no statistically significant difference in childhood height.

## **Conclusions**

IVF/ICSI were not associated with long-term weight and height.

## **Funding**

None.

## Key Words:

Infertility; Assisted reproduction; Child development; Height; Weight

## Tweetable abstract:

Children born following IVF/ICSI do not have impaired long-term weight or height compared with spontaneously conceived children.

## Introduction

During the last decades, several studies have shown that infants born following assisted reproductive techniques (ART) have an increased risk of adverse pregnancy outcomes<sup>1</sup>.

Although the complications are partly related to the higher risk of multiples due to transfer of more than one embryo, even singletons conceived after *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) have a higher risk of being born with a lower birth weight, shorter gestational age, and higher risk of being small for gestational age<sup>2</sup> compared to spontaneously conceived singletons.

The aetiology and physiological mechanism of the impaired intrauterine growth is largely unknown. Yet, long-term follow-up on the growth of these children is limited and inconsistent. Several studies suggest that the impaired growth during the intrauterine life is caught up in early childhood<sup>3-8</sup>. However, other studies show that height or weight continue to be lower compared to spontaneously conceived children suggesting that the metabolism of ART children may be permanently altered<sup>9-11</sup>. IVF and ICSI were introduced in 1978 and 1981, respectively, and as this cohort of children grow older, it is important to continuously monitor their health and development. On the long-term, impaired intrauterine growth as well as early neonatal catch-up growth has been shown to be associated with a risk of morbidity later in life<sup>12-14</sup>. Thus,

studies on the post-neonatal growth of children born following IVF or ICSI treatment is of imminent importance.

We aimed to systematically review the existing literature on post-neonatal height and weight of children conceived following IVF or ICSI treatment compared to spontaneously conceived children. To evaluate the hypothesis that the lower birth weight among children born following IVF or ICSI is no longer apparent later in childhood, we conducted meta-analyses on the association between IVF/ICSI and child weight and height.

## **Methods**

### *Study Selection*

Studies assessing child weight or height beyond the neonatal period were collected by a systematic computerized literature search using the online databases Pubmed/Medline, Embase, and Scopus. The initial data search was performed 18 October 2016 and repeated 12 June 2017 before finalization of the manuscript. Key words were used to identify potential, relevant studies as listed in Table 1. Additionally, free text search was performed, and the bibliography of included studies were hand searched to include additional studies or studies not yet indexed in the databases.

Studies were considered potentially eligible for inclusion if they were cohort or case-control studies. The studies had to include an exposed group of singletons conceived following IVF or ICSI treatment along with a control group of spontaneously conceived singletons. We considered studies eligible if they conducted follow-up on height or weight of the children beyond the neonatal period measured on a continuous scale. If more than one follow-up point were available for a study (i.e. at different ages), only the most recent was included for analysis since the main objective of the meta-analyses was to evaluate long-term growth. Hence, the

timing of any postnatal catch-up growth was considered outside the scope of this study. The searches were not restricted by any limitation to study year, geographic location, or ethnicity, but the language was confined to English. Studies were excluded if they were case series, case reports, were lacking a reference group of spontaneously conceived children, or the exposed group was limited to donor insemination, surrogacy, ovulation induction, or intrauterine insemination.

All identified studies were screened by titles and abstracts for eligibility. Potentially relevant studies were obtained and read in full text and critically evaluated for inclusion.

#### *Data extraction and quality assessment*

Information from each of the included studies was consistently summarized using an *a priori* specified data extraction form covering design, population, exposure and outcome assessment, age of the children, blinding, bias, and results. All studies were reviewed by at least two authors. Any differences were settled by discussion by the reviewing authors for a given study. If disagreement persisted, an additional author was consulted. The quality of the included studies was assessed with the Newcastle-Ottawa Scale<sup>15</sup> as recommended by the Cochrane Non-Randomized Studies Methods Working Group. This assessment scores the selection, comparability, and ascertainment of exposure and outcome and summarizes the quality with a total score between 0 and 9. The scoring of each study was blindly conducted by at least two authors independently and discussed if any inconsistency occurred. We defined studies with a score of 7 or above as “high-quality studies”. This review follows the PRISMA statement<sup>16</sup> for the preferred reporting of systematic reviews and meta-analyses but was not preceded by a review protocol. No core outcome set (COS) was available for the outcomes of this review and the study was conducted without patient involvement.

### *Statistical analyses*

For the quantitative meta-analyses we used the Cochrane meta-analyses software Review Manager version 5.3<sup>17,17</sup>. The mean and standard deviation of height and/or weight for each included study were extracted and entered into the software along with information on first author, year of publication, and number of exposed children and controls. If other outcome measures of height or weight than means and standard deviations (e.g. medians, standardized scores, or percentiles) were reported in a study, the authors were contacted by email with a request for means and standard deviations. In the case of no response or unavailable data, medians and ranges were converted to means and standard deviations assuming Gaussian distribution of height and weight using a standard formula<sup>18</sup>. Other continuous outcome measures of child weight or height (e.g. standardized scores; percentiles) were left unconverted, and studies reporting such measures were only included in the review in a narrative format and thus excluded from the meta-analyses.

All analyses were performed using random effect models, assuming that the true effect size varies between studies, and that the studies in our analysis represent a random sample of effect sizes. In the main meta-analyses on childhood height and weight, we included all studies with reported means and standard deviations and studies with medians and ranges converted to means and standard deviations. For studies reporting outcome information on IVF and ICSI children separately, a pooled weighted mean and standard deviation was calculated for the main analyses. Similarly, a combined mean and standard deviation was calculated if the results were reported for girls and boys separately assuming no effect modification by child gender. Since the main meta-analyses were conducted assuming Gaussian distribution of height and weight allowing for conversion of medians and ranges to means and standard deviations, we conducted sensitivity analyses only including studies with reported means and standard deviations (or if the authors were able to supplement with such information after e-mail contact). Additionally, we conducted analyses only including studies evaluated as “high quality



studies" (7 or more point on the NOS) and analyses stratifying child age into two pre-specified groups (0-4 years; 5+ years) based on previous research suggesting comparable weight among 5-year-old singletons born following fertility treatment and spontaneous conception<sup>19</sup>. Finally, analyses of IVF and ICSI were conducted separately in order to explore whether any potential association with childhood height or weight was restricted to either of these exposures. All results were summarized in Forest plots, while evaluating a possible between-study heterogeneity with  $I^2$ . An  $I^2$  of less than 40% was considered as evidence of low risk of heterogeneity<sup>20</sup>.

## **Funding**

This project was initiated by the authors and was not conducted under specific funding.

## **Results**

A total of 297 potentially relevant studies were identified through database and bibliography searches. After screening of titles and abstracts 241 studies were excluded and the remaining 56 papers were obtained and critically appraised in full text. Studies with irrelevant outcomes, no control group, no specific outcome information on singletons, or studies only published as conference abstracts were excluded leaving 20 studies available for the systematic review and meta-analyses including children up to the age of 28 years (Figure 1) (Table S1). Of these, ten studies<sup>4-7, 21-26</sup> reported growth outcomes in means for height and/or weight. The authors of the remaining ten studies were contacted by email with a request for the means and standard deviations for weight and/or height. The authors of two studies<sup>27, 28</sup> were able to supply the means and standard deviations. Further, one of the remaining studies reported the growth outcomes in medians and ranges and assuming Gaussian distribution of these outcomes the

outcome measures were converted to means and standard deviation<sup>18</sup>. Thus, we were able to include 13 studies in the meta-analyses. The remaining seven studies were included as a narrative review and described below<sup>8-11, 29-31</sup>.

#### *Quality of the included studies*

In general, the main methodological limitations of the included studies were lack of sufficient control for potential confounders and lack of blinded assessment of growth outcomes. For the quality assessment, use of the Newcastle-Ottawa-Scale requires selection of the most important confounding factor for the association in question. We considered the most important covariate parental anthropometrics (weight, height, or body mass index) and only six studies took one or more of these variables into account in the analyses<sup>3, 8-10, 23, 26</sup>. Similarly, very few studies included objective assessment of weight and/or height blinded for the exposure<sup>5, 24, 31</sup>. Nevertheless, the included studies were generally well conducted, ranging from 4 to 9 in total score on the Newcastle-Ottawa-Scale, with an average score of 6.6 (SD 1.4) and a median of 7. Using a cut-off at 7 points, a total of 11 studies were categorized as “high-quality” studies and included in the sensitivity analyses below.

#### *Meta-analyses of childhood weight*

Children conceived following IVF/ICSI treatment did not have a statistically significant lower weight compared to spontaneously conceived controls (Figure 2). The meta-analysis compared 3,972 IVF/ICSI children with 11,012 spontaneously conceived children up to a maximum mean follow-up time of 22 years and revealed a mean difference (MD) in weight of -160 grams (95% CI: -360; 3) with low risk of heterogeneity ( $I^2=39\%$ ). The results were robust in sensitivity analyses only including studies originally reporting means and standard deviations or studies where the authors were able to supply such upon request (MD -160 grams (95% CI: -370; 5),

$I^2=44\%$ ). Similar, when only assessing studies categorized as “high-quality”, the conclusion remained unchanged (MD -70 grams (95% CI: -300; 150),  $I^2=19\%$ ).

When stratifying on child age at follow-up, we found a significant lower weight of children conceived following IVF/ICSI treatment, but only up to preschool age. Compared to spontaneously conceived children 0-4 years old, children conceived following IVF/ICSI treatment had a statistically significant lower weight (MD -180 grams (95% CI: -320; -4),  $I^2=0\%$ )(Figure S1). Beyond this age, the difference in weight was no longer significant although the confidence interval was considerable larger (5+ years, MD -160 grams (95% CI: -580; 260),  $I^2=52\%$ ).

Finally, we performed meta-analyses stratified on conception mode (IVF or ICSI treatment, respectively). Compared to spontaneously conceived controls, children conceived following IVF treatment had a lower, although statistical insignificant weight (MD -210 grams (95% CI: -730; 310),  $I^2=74\%$ ). Similar, the weight of children following ICSI treatment was comparable to that of the controls (MD -150 grams (95% CI: -350; 60),  $I^2=0\%$ ).

#### *Meta-analyses of childhood height*

The meta-analysis of childhood height among children conceived following IVF/ICSI treatment compared to spontaneously conceived controls are presented in Figure 3. The pooled analysis revealed no statistically significant difference in childhood height among the eligible studies (MD 0.13 cm (95% CI: -0.20; 0.47),  $I^2=24\%$ ). Similar results were found in the sensitivity analyses of “high-quality” studies and studies categorizing the exposure into IVF or ICSI treatment, respectively. Furthermore, meta-analyses of child height categorized according to age of the child did not reveal any association with conception following IVF/ICSI treatment for the age group 0-4 years (MD 0.10 cm (95% CI: -0.69; 0.49),  $I^2=40\%$ ) or later in childhood (MD 0.27 cm (95% CI: -0.15; 0.68),  $I^2=17\%$ ).

### *Heterogeneity and publication bias*

For all performed meta-analyses, we detected a low to moderate risk of between-study heterogeneity. The risk of publication bias was analysed using visual inspection of funnel plots in meta-analyses including at least 10 studies with no apparent evidence of publication bias.

### *Studies not eligible for meta-analyses*

A total of seven of the included 20 studies did not report child weight and/or height in means and standard deviations in the published paper or upon request to the author<sup>8-11, 29-31</sup>. The age of the children in these studies ranged from 1.5 years to 6.4 years. The majority of the studies did not show any association between conception following IVF or ICSI and childhood weight and height<sup>8, 29-31</sup>. However, a few studies found larger height in childhood among children exposed to IVF compared to spontaneously conceived controls. Miles et al. conducted a follow-up on 35 IVF children, 34 ICSI children, and 71 naturally conceived controls between 4 and 10 years of age, born in New Zealand between 1995 and 2000. The study showed that IVF children were taller than spontaneously conceived controls and remained so when adjustment was made for age and parents' heights with the difference being most evident in girls<sup>10</sup>. As an expansion of this study, Green et al. compared the height and weight of 115 children conceived following IVF, born between 2004 and 2008 with that of 94 spontaneously conceived controls, born between 1993 and 2005<sup>9</sup>. Although, the spontaneously conceived children were slightly older than the IVF children, the IVF children were again found to be significantly taller. When embryo treatment (fresh versus thawed) and child gender were accounted for, the results were only significant for the fresh IVF treatment and for the girls (approximately 2.5 cm taller than controls). Similarly, another Australian study by Saunders et al. showed that the length among 2-year-old IVF children compared to spontaneously conceived controls were significantly longer (mean length percentile 57.7 (95% CI 54.4; 61.0) compared with 49.9 (95% CI 45.5; 54.3) for the controls). No differences were found for weight or head circumference<sup>11</sup>.

## Discussion

### *Main Findings*

This review and meta-analysis systematically evaluated the long-term weight and height of children conceived following IVF or ICSI compared to that of spontaneously conceived controls. In the pooled analyses, we found a slightly lower weight in childhood, although not statistically significant and less likely of any clinical significance. When stratifying on child age at follow-up, we found a statistically significantly lower weight of children conceived following IVF/ICSI treatment, but only up to preschool age. In contrast, the long-term height was unaffected with comparable results between IVF/ICSI treatment and spontaneously conceived children. Overall, these results were supported by the studies included in this review, not eligible for meta-analysis. Although a few small studies showed slightly taller height among children conceived following IVF<sup>9-11</sup>, most studies found no difference in height or weight.

### *Strengths and Limitations*

Overall, the methodological quality of the included studies was high, which was reflected in a median NOS score of 7 (range 4-9). However, some limitations of the included studies must be emphasised. While the selection of the exposed group of children conceived following IVF or ICSI treatment was generally representative in the vast majority of studies, the selection of controls was questionable in a few studies. In one study, controls were included partly from a pediatric practise<sup>23</sup> and in another study partly after advertising<sup>3</sup>. In a third study, the controls were made up of a group of children born by parents conceiving naturally, but after a long waiting time to pregnancy<sup>4</sup>. While using a group of children conceived by subfertile parents may be valid in order to distinguish an adverse effect of the IVF procedure from the subfertility *per se*, it may be considered less representative in this setting and certainly different from the other included studies. Finally, in one of the studies included in this review, 32 of the 66 children in

the reference group were conceived following ovulation induction<sup>31</sup>. Such misclassification could lead to an underestimation of the potential association between IVF treatment and long-term growth if children born following ovulation induction were at risk of impaired growth pattern in childhood.

In all studies but one, the analyses of childhood weight or height were controlled for potential confounders. In most studies, these variables included socioeconomic factors, maternal age, and parity. However, only few studies included measures of parental anthropometrics in the analyses. The importance of adjusting for this key covariate was illustrated in a multicentre study from Belgium, Sweden and USA<sup>3</sup>. In this study, children conceived after ICSI treatment were significantly taller than spontaneously conceived peers. However, the difference was not significant after adjustment for parental height, which was, unfortunately, only possible for the Swedish cohort.

In contrast, several studies performed conditioning on birth weight by use of matching in the selection of controls or adjusting for birth weight in the statistical analyses<sup>10, 23, 26, 31</sup>. Since IVF and ICSI are associated with risk of low birth weight, birth weight may be considered to be on the causal pathway between fertility treatment and long-term growth. Conditioning on intermediate variables such as birth weight may introduce bias - typically towards the null<sup>32</sup>, which may partially explain the conclusions in some of the studies.

Several of the included studies were limited by a small sample size or a low participation rate down to 25%<sup>22</sup>. This may potentially have biased the results due to a tendency to include and assess children with normal development if children with impaired growth were more prone to decline participation in follow-up.

For the three studies reporting results for boys and girls separately, we pooled these results for the meta-analyses<sup>4, 7, 26</sup>. Although the age-specific weight and height are different for boys and girls, we do not expect that this could have affected the conclusions of our analyses since the

conclusions remained unchanged when the meta-analyses were performed on boys and girls separately for these studies (data not shown).

### *Interpretation*

Singletons born after fertility treatment have been shown to have lower birth weight compared to spontaneously conceived children<sup>2</sup>. In general, impaired fetal growth and postnatal catch-up may be related to increased risk of obesity, cardiovascular disease, and diabetes later in life<sup>12-14</sup>. Specific for IVF children, a rapid weight gain during childhood has been associated with higher blood pressure independently of birth weight, gestational age and body size at follow-up in 8-18-year-old children<sup>33</sup>.

Adverse health outcomes in offspring conceived following ART are likely to be multifactorial. Although, the largest risk is associated with the higher frequency of multiples, even singletons have increased risk of adverse outcomes. A considerable proportion of these risks are likely to be associated with parental factors including the subfertility *per se* and any causes thereof<sup>2</sup>. Nevertheless, several of the specific parts of in vitro fertilization have been associated with adverse outcomes in the offspring, some of which may be due to ovarian stimulation, culture medium, freezing-thawing process, vanishing twins, or even more precautionous obstetric management with more induced labour or caesarean sections on vague indications<sup>2</sup>.

While the focus of this review was long-term height and weight, the evaluation of a potential time point of catch-up was not the objective. Instead, we chose to utilize the data from the final observation if several follow-up points were reported. Additionally, this method avoids violating the assumption of independence for statistical inference. However, based on an *a priori* determined analyses plan we performed stratified analyses categorizing the studies into groups based on the age of the children at follow-up. While also ensuring potential

normalization of any altered intrauterine and early life metabolism among IVF/ICSI children, the age categories were additionally based on previous research showing that the weight of 5-year-old singletons conceived following fertility treatment was comparable to controls despite lower birth weight<sup>19</sup>. Due to the number of studies eligible for meta-analyses we did not consider more than two groups. These stratified analyses showed some evidence of a time of catch-up at child age less than 5 years. However, the exact time of catch-up on the lower birth weight seen in children conceived following IVF/ICSI may be earlier in childhood or even infancy<sup>8</sup>. Despite evidence of differences in birth weight, several of the included studies reported comparable growth outcomes later in childhood or adolescence for singletons born by parents conceiving after IVF or ICSI compared with spontaneously conceived controls<sup>3-8</sup>. These results suggest that IVF/ICSI children have an increased postnatal growth velocity, which is supported by the conclusions from this review and meta-analyses. However, since only few studies included children beyond the age of preschool, these results must be interpreted with caution.

## Conclusions

In conclusion, this review and meta-analysis showed no impact of assisted reproduction on long-term child growth. Although IVF/ICSI were negatively associated with childhood weight, the differences were small, below clinical significance, and only up to the age of pre-schoolers. These results suggest that the lower birth weight found in children conceived following IVF/ICSI is not present later in childhood. However, this review did not investigate an exact timing of a post neonatal catch-up growth. Childhood height was found to be unrelated to mode of conception. Additional and longer-term follow-up on the growth and metabolism of children born following IVF, ICSI, as well as non-ART treatments is still needed.



### **Details of ethics approval**

Not applicable.

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None.

### **Disclosure of interests**

USK reports personal fees from Ferring and Merck Sharp A/S, unrelated to the submitted work. All other authors declare no competing interests. Completed disclosure of interest forms are available to view online as supporting information.

### **Contribution to authorship**

BB, JL, LH, and USK contributed to conception and design of the study and acquisition of data. BB conducted the analyses and BB, JL, LH, and USK contributed to the interpretation of the results. BB performed the drafting of the manuscript and BB, JL, LH, and USK have been revising it critically for important intellectual content, and finally approving the version to be published.

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## FIGURE LEGENDS:

Figure 1. Flowchart for the selection of included studies.

Figure 2. Forest plot comparing childhood weight among children conceived following in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) with spontaneously conceived children (SC) using a random effect model.

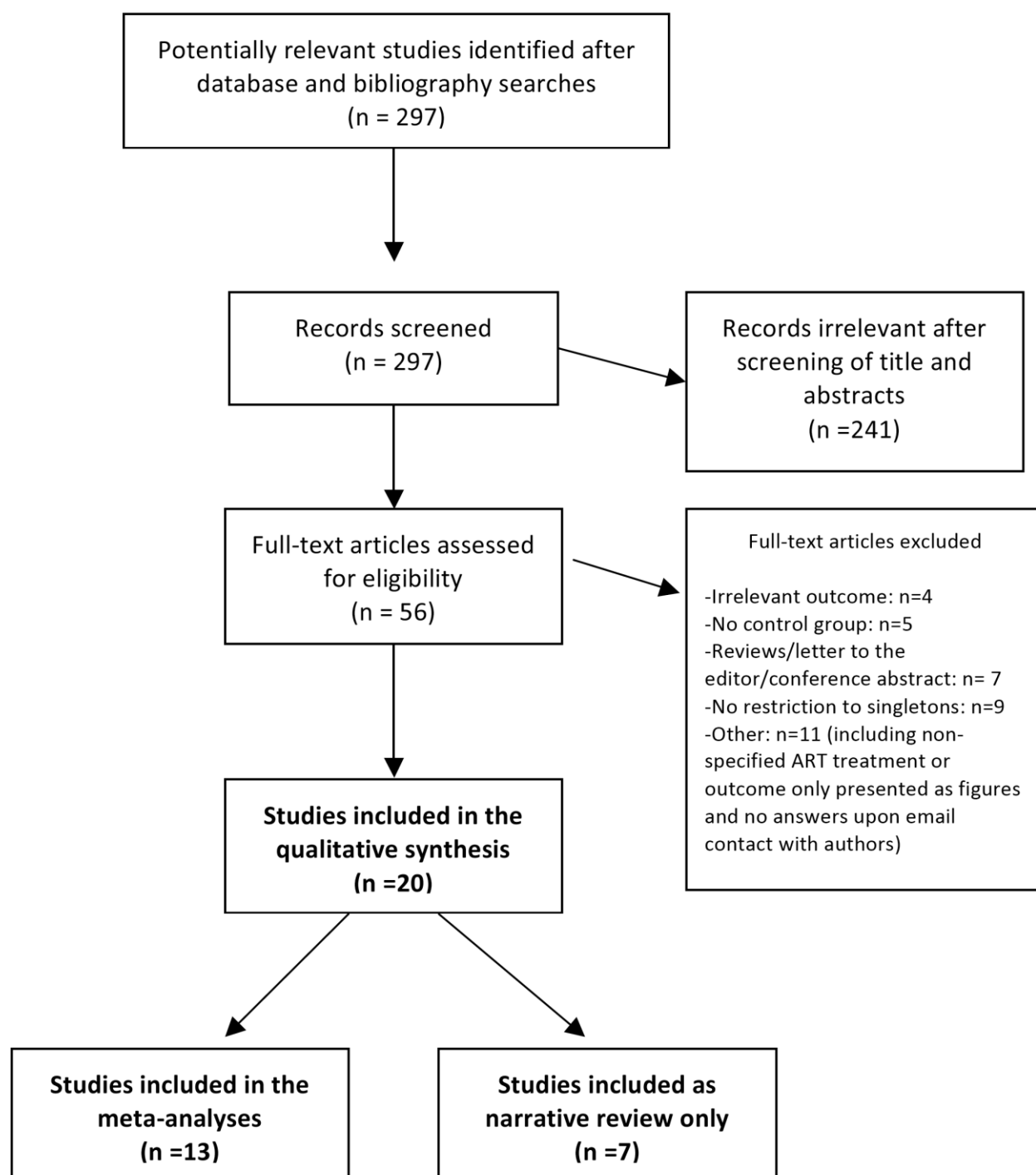
Figure 3. Forest plot comparing childhood height among children conceived following in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) with spontaneously conceived children (SC) using a random effect model.

Figure S1. Forest plot comparing childhood weight among children less than 5 years old conceived following in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) with spontaneously conceived children (SC) using a random effect model.

**Table 1.** Criteria for search and selection of eligible studies

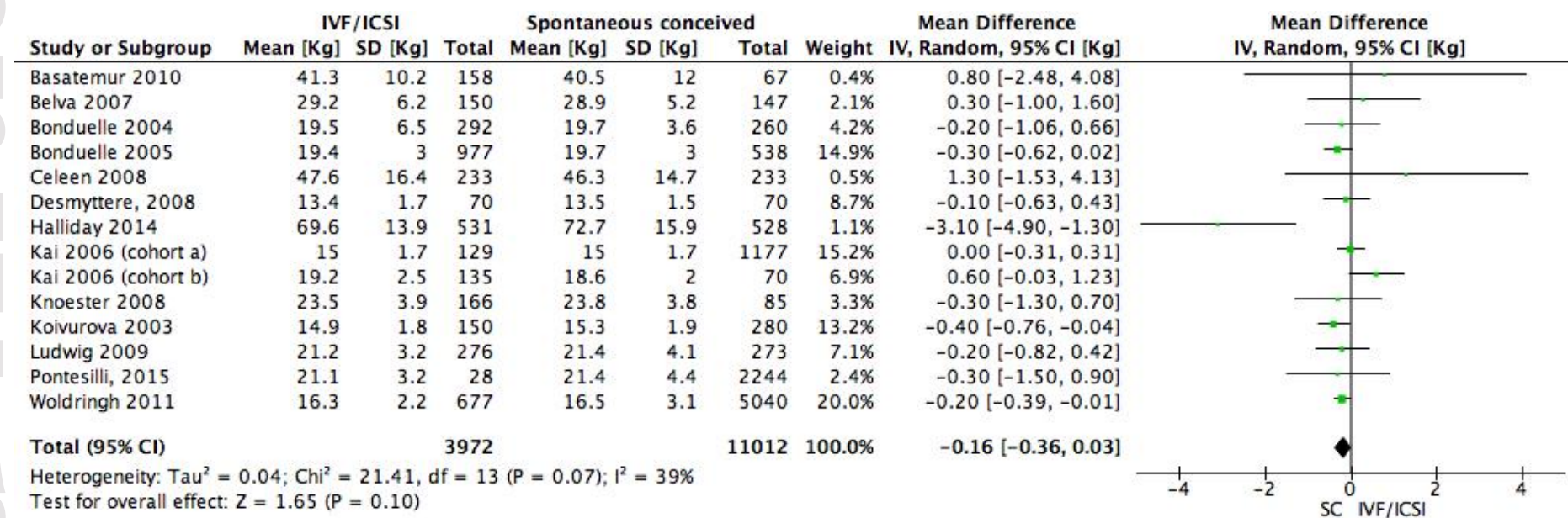
CRITERIAS	
Date of literature search	18 October 2016 (repeated on 12 June 2017)
Databases	PubMed, Embase, Scopus, and bibliographies of included studies
MESH	("Reproductive Techniques, Assisted") AND (("Child Development") OR ("Adolescent")) AND (("Body Weight") OR ("Body Height") OR ("Body Mass Index") OR ("Growth") OR ("Growth and Development"))
Year	No limits
Language	English
Outcomes	Postnatal height and weight (beyond neonatal period of first 4 weeks of life)
Study designs	Case-control, cohort
Inclusion criteria	<p>1) Singletons</p> <p>2) If more than 1 follow-up was reported (e.g. different ages), only the longest is chosen for analysis for the following reasons: i) focus is on long-term follow-up <i>and</i> ii) the timing of postnatal catch-up growth is outside the scope of this meta-analysis</p> <p>3) Only specified exposure (In vitro fertilization or intracytoplasmic sperm injection)</p> <p>4) If another outcome measure than mean (SD) were reported the authors were contacted. In the case of no response or unavailable data, any medians (ranges) were converted to means and standard deviations (SD) assuming Gaussian distribution of height and weight. Other outcome measures (i.e. percentile scores) were not converted and studies with such measures were only included in the review in a narrative format and thus excluded from the meta-analyses.</p>
Exclusion criteria	Case series; case reports; lack of reference group of spontaneously conceived children; exposed group limited to donor insemination, oocyte donation, surrogacy, ovulation induction, intrauterine insemination.

Meta-analyses	<p><i>Main analysis:</i></p> <p>Including all studies with reported means (SD) or converted medians (ranges)</p> <p><i>Sensitivity analyses:</i></p> <ol style="list-style-type: none"><li>1) Only including studies with reported means (SD) or where the authors were able to supplement with means (SD) after email contact</li><li>2) Only including studies assessed as “high quality studies” (7 or more point on the NOS)</li><li>3) Stratified analyses according to child age groups (0-5 years; 6+ years)</li><li>4) Stratified analyses according to treatment type (IVF; ICSI)</li></ol>

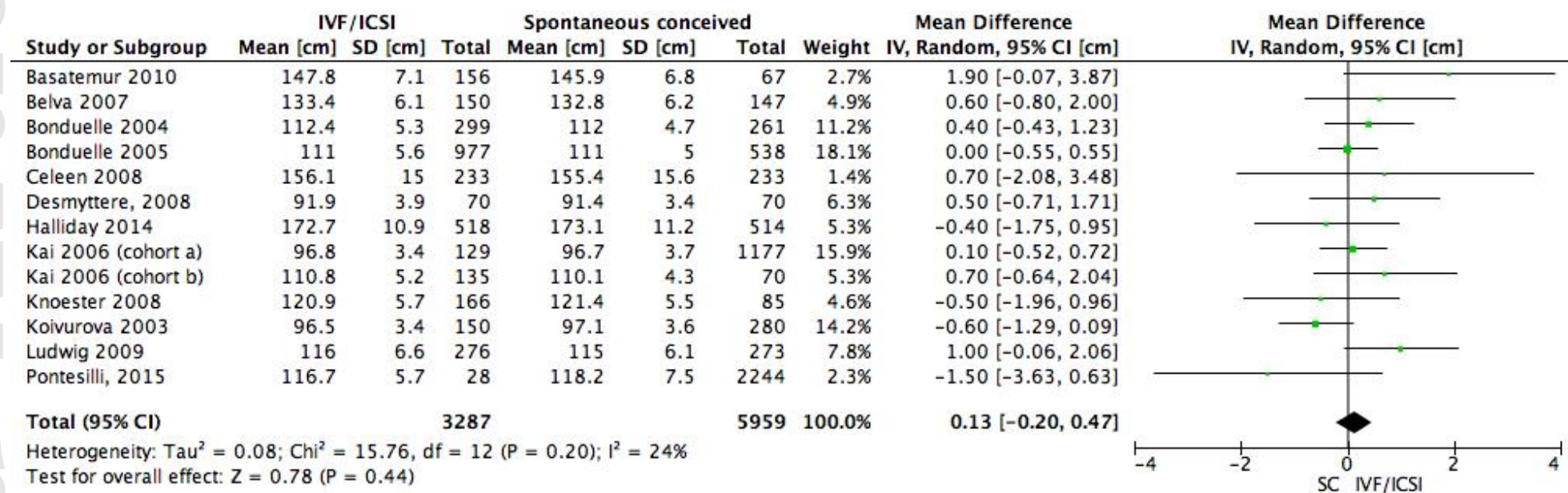


**Figure 1.** Flowchart for the selection of included studies.





**Figure 2.** Forest plot comparing childhood weight among children conceived following in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) with spontaneously conceived children (SC) using a random effect model.



**Figure 3.** Forest plot comparing childhood height among children conceived following in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) with spontaneously conceived children (SC) using a random effect model.